

REMARKS

Claims 1-60 are pending in this application, with claims 1-21 and 35-47 having been withdrawn from consideration pursuant to a restriction requirement. As such, claims 22-34 and 48-60 have been examined on the merits.

The Examiner's attention is directed to the IDS filed May 12, 2003. With this response the fee is paid to secure consideration of this IDS.

A. Effective Priority Date

The Examiner stated that the effective priority date of this application is January 29, 2001. Applicants respectfully traverse and submit that the effective priority date for many of the pending claims is November 2, 1992, which is filing date of the earliest claimed priority application.

At the outset, Applicants respectfully submit that the determination of an effective priority date must be made on a claim by claim basis. MPEP 706.02. Therefore, claims which are fully supported under 35 U.S.C. § 112 by the earlier parent application have the effective filing date of the earlier parent application. MPEP 706.02.

The Examiner based his determination of the January 29, 2001 effective filing date on his finding that the claimed dry formulations wherein the microbubbles comprise SF₆ and the straight chain saturated fatty acid is arachidic, behenic or lignoceric acid was not disclosed in the parent cases. However, assuming that to be true, only claims 26 and 52 contain these arachidic, behenic or lignoceric acid limitations and thus only claims 26 and 52 would have an effective filing date of January 29, 2001. All other examined claims (*i.e.*, 22-25, 27-34, 48-51, and 53-60) are fully supported in the earliest parent application (*e.g.*, pp. 5, 6, 9-11) and therefore one skilled in the art would recognize that Applicants was in possession of the claimed invention as of November 2, 1992 and thus have an effective filing date of November 2, 1992.

B. Applicants Claims Are Patentable Over The Cited Art

Claims 22-34 and 48-60 were rejected under 35 U.S.C. § 103(a) over U.S. Pat. No. 5,599,523 (“Beller”) in view of U.S. Pat. Nos. 5,542,935 (“Unger”), 5,529,766 (“Klaveness”), and 5,393,524 (“Quay”). Applicants respectfully traverse.

C. Unger Is Not Prior Art To Schneider Claims 22-25, 27-34, 48-51, and 53-60

As explained above, pending claims 22-25, 27-34, 48-51, and 53-60 have an effective priority date of November 2, 1992, the filing date of EP 92810837. Applicants observe that Unger mentions some seven or more U.S. priority filing dates, most of which are continuation-in-part applications which continue to add new matter to each previous priority application. Yet the Examiner does not specify which of these dates is being relied upon in the Office Action. Applicants believe that the earliest possible effective filing date under 35 U.S.C. 102(e) is thus November 30, 1993 and respectfully request the Examiner to confirm this determination. Thus, withdrawal of this rejection based on Unger is respectfully requested. Applicants also address the merits of the rejection based on Unger below for completeness.

D. Applicants’ Claims 22-34 And 48-60 Are Nonobvious And Patentable Over Beller In View Of Klaveness, Unger And Quay

None of the cited references, by itself or in any proper combination with another reference, discloses each of the limitations of Applicants’ claims 22-34 and 48-60. Therefore, all of Applicants’ pending claims are novel and nonobvious over the cited references.

1. Applicants’ Claimed Invention Is Directed To Dry Formulations

Applicants’ broadest claim 22, *inter alia*, requires the following:

- (1) a dry formulation of an ultrasound contrast agent
- (2) comprising

- (a) a saturated phospholipid,
 - (b) a fatty acid and
 - (c) a hydrophilic stabilizer
- (3) which upon dissolution in an aqueous carrier liquid forms a suspension of micrubbles comprising SF₆
- (4) wherein the amount of saturated phospholipid in the suspension is less than about 0.01% by weight.

Thus, at the very minimum, in order for Applicants' broadest claim to be found unpatentable, the cited references must each or collectively within the guidelines for determining obviousness, disclose or suggest each of the elements set forth above. Applicants respectfully submit that the combination cited by the Examiner is not only improper, but also fails to disclose or suggest all of elements (1), (2), (3) and (4) of the claimed invention. Thus, as Applicants' broadest claim 22 is patentable over those references, so are the rest of Applicants' claims.

2. Beller Is Directed To Aqueous Formulations

Beller discloses an aqueous preparation for receiving and stabilising micro gas bubbles. Abstract; col. 1, lines 9-10, lines 43-45; claims 1-24. There is no disclosure or suggestion in Beller of a dry formulation of an ultrasound contrast agent or of the Applicants' claimed combination of a saturated phospholipid, a fatty acid, and a hydrophilic stabilizer. In fact, each of Beller's examples teaches to mix pluronic, a phospholipid such as dipalmitoylphosphatidylglycerol, and glycerol into water to form Beller's claimed aqueous preparation for receiving and stabilising micro gas bubbles. Col. 2, line 62 - col. 3, line 23. No gas bubbles are formed upon dissolution of these ingredients in water. *Id.* It is not until air is subsequently added in a mixing chamber and mixed that micro gas bubbles are finally formed. Col. 3, lines 47-55.

Furthermore, as the Examiner admits, Beller does not teach or suggest the use of SF₆ gas.

Beller also fails to teach or suggest the use of saturated phospholipids in an amount less than 0.01% by weight of the suspension. As the Examiner notes, Beller teaches 0.01 to 5% weight/volume of phospholipids. Col. 1, lines 56-59. However, Beller also teaches that it is preferable to use 0.5 to 2% by weight phospholipids - in other words Beller teaches away from lowering its phospholipid concentration to the limitation claimed by Applicants.

Therefore, Beller itself fails to teach or suggest any of the elements 1-4 as listed in Section D.1. For the claims to be obvious over the combination of references cited by the Examiner, the remaining references must teach or suggest, within the guidelines set for obviousness analysis, one of ordinary skill in the art to modify Beller to incorporate each of those missing elements.

As explained below, the references relied upon by the Examiner fail to provide the necessary incentive or motivation to combine them in an attempt to create the Applicants' claimed invention. There is nothing in any of the references to suggest the desirability of the combination or further the modification in the manner indicated by the Examiner. Furthermore, even if the combination or modification was somehow suggested, the references fail to disclose each of the limitations of the Applicants' claims. Thus, Applicants respectfully request that this rejection be withdrawn.

3. There Is No Suggestion In The Cited References To Combine

It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead one of ordinary skill in the art to combine those references. *In re Dembicza*k, 50 U.S.P.Q.2d 1614, 1617-18 (Fed.Cir. 1999) ("Our case law makes clear that the best defense against the subtle but

powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.”)

Merely asserting that it would have been within the skill of the art to substitute one type of gas for another in the contrast agent of the primary reference is not enough. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed.Cir. 1988)(Holding that there was no support for the Examiner’s mere assertion that it would have been obvious to substitute one type of detector for another in the system of the primary reference); *In re Jones*, 21 U.S.P.Q.2d 1941 (Fed.Cir. 1992)(Holding that there was no suggestion to combine a primary herbicide reference with secondary references directed to shampoo additives or byproducts of morpholines to arrive at the claimed invention.); MPEP § 2143.01.

There is nothing in any of the cited references to suggest the desirability of the combination or modification in the manner indicated by the Examiner. Specifically, there is no motivation or suggestion to combine Beller with Unger, Klaveness or Quay because they are all directed toward completely different types of contrast agents. The mere fact that the contrast agents disclosed in Beller, Unger, Klaveness and Quay may be used for ultrasonic imaging does not make them the same as or analogous to each other.

Unger is directed to temperature activated gaseous precursor filled microspheres wherein the gaseous precursor becomes a gas only upon activation at a selected temperature. *E.g.*, col. 4, lines 29-31; col. 6, lines 52-55, col. 7, lines 57-60. Thus, Unger’s invention requires an “activation” to turn its gaseous precursor filled microspheres into gas filled microspheres. Unlike Unger, Beller’s microbubbles are not gaseous precursor filled nor are they “activated” to turn the gaseous precursors into gas filled microbubbles.

Klaveness is directed to microbubbles of gas or gas precursors encapsulated in a shell of protein crosslinked with biodegradable crosslinking groupings. *E.g.*, col. 3, lines 12-16. Unlike Klaveness, Beller's microbubbles are not encapsulated with protein, nor are they crosslinked with biodegradable crosslinking groupings.

Quay is directed to free gas microbubbles which do not have any type of shell, envelope, or stabilizers around the gas bubble. *E.g.*, col. 1, lines 15-18; col. 5, lines 5-20; claims 1-13. Beller's microbubbles are not free gas microbubbles.

Therefore, one of ordinary skill in the art thus will not be motivated to combine Beller with the different temperature activated gasesous precursor filled liposomes of Unger, or with the crosslinked protein microbubbles of Klaveness, or the free gas microbubbles of Quay since they are directed toward completely different inventions.

4. The Mere Fact That References Can Be Modified Or Combined Is Not Enough

Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-1784 (Fed. Cir. 1992)(emphasis added):

The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification.

Thus, the mere fact that references can be combined or modified (and Applicants believe they cannot) does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed.Cir. 1990); MPEP § 2143.01.

Furthermore, the Applicant's own disclosure cannot be used in an obviousness analysis. *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent

in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.""); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.") Hence, as explained below, the Examiner's proposed modification to Beller is improper in the absence of any suggestion in the references of the desirability of the modification and thus, this rejection should be withdrawn.

a. Unger

The Examiner relies on Unger for the following three teachings: (a) the use of fatty acids such as palmitic acid, (b) the hydration/lyophilization of lipids and (c) the use of SF₆ gas. Office Action, pp. 4-5.

Specifically, there is no teaching or suggestion in Unger to motivate one of ordinary skill in the art to selectively choose these three specific teachings of Unger to modify Beller in the manner described by the Examiner. MPEP § 2143.01. For example, while fatty acids are mentioned in Unger, there is no teaching or suggestion in Unger that it is preferable to use fatty acids such that one of ordinary skill in the art would be motivated to add that substance to Beller's composition, nor is there any teaching or suggestion that palmitic acid should be the specific fatty acid chosen from within a laundry list of fatty acids which can be used. Col. 22, lines 35-48.

Additionally, while the hydration and lyophilization of lipids is disclosed in Unger, there is no teaching or suggestion in Unger that it is preferable to hydrate and lyophilize phospholipids such that one of ordinary skill in the art would be motivated to disregard Beller's teaching for an aqueous preparation and form dry formulations, much less Applicants' specifically claimed dry formulation ingredients. Col. 40, lines 5-25.

Finally, while Unger discloses the use of SF₆ gas, there is no teaching or suggestion in Unger that it is preferable to use SF₆ gas such that one of ordinary skill in the art would be motivated to specifically choose SF₆ from within a laundry list of twelve other gases in the example cited by the Examiner. Col. 67, lines 8-13. Rather, Unger teaches that it is preferable to use perfluorocarbons, not SF₆. Col. 17, lines 17-23. Thus, Unger teaches away from the modification proposed by the Examiner.

Without any such proper teaching or suggestion, these modifications chosen by the Examiner could only be the result of impermissible hindsight based on Applicants' disclosure. MPEP § 2142. As such, withdrawal of this rejection is respectfully requested.

b. Klaveness

The Examiner relies on Klaveness for teaching the use of SF₆ gas. Office Action, p. 4.

While Klaveness discloses the use of SF₆ or low molecular weight fluorinated hydrocarbon gas, there is no teaching or suggestion in Klaveness that it is preferable to use SF₆ gas such that one of ordinary skill in the art would be motivated to specifically choose SF₆ instead of a low molecular weight fluorinated gas. Abstract, claims 1-10.

Without any such proper teaching or suggestion, this selective modification chosen by the Examiner could only be the result of impermissible hindsight gleaned from the Applicants' disclosure. MPEP § 2142. As such, withdrawal of this rejection is respectfully requested.

c. Quay

The Examiner relies on Quay for teaching the use of SF₆ gas. Office Action, p. 4.

While Quay discloses the use of SF₆ gas, there is no teaching or suggestion in Quay that it is preferable to use SF₆ gas such that one of ordinary skill in the art would be motivated to specifically choose SF₆ instead of any of the other eight (8) gases which have a Q coefficient higher than 30. Col. 14, Table II. Rather, since Quay teaches that higher Q coefficients

purportedly are more stable than those with lower Q coefficients, one of ordinary skill in the art would be motivated to at least choose the four other gases which have significantly higher Q coefficients than SF₆. Col. 12, lines 58-63. Thus, Quay teaches away from the modification proposed by the Examiner.

Without any such proper teaching or suggestion, this selective modification chosen by the Examiner could only be the result of impermissible hindsight gleaned from the Applicants' disclosure. MPEP § 2142. As such, withdrawal of this rejection is respectfully requested.

5. The Modification Cannot Change
The Principle Of Operation Of A Reference

The proposed modification cannot change the principle of operation of a reference. *In re Ratti*, 123 U.S.P.Q. 349 (C.C.P.A. 1959); MPEP § 2143.01. However, the Examiner's proposed modification would effectively change the principle of operation of each reference.

Unlike Unger, Beller's microbubbles are not gaseous precursor filled nor are they "activated" to turn gaseous precursors into gas filled microbubbles. Beller's microbubbles are also not encapsulated with protein, nor are they crosslinked with biodegradable crosslinking groupings like Klaveness, nor are they free gas microbubbles like Quay.

Thus, Beller's microbubbles have different principle of operation from the inventions of Unger, Klaveness and Quay. As such, since the Examiner's proposed modification would thus improperly change the principle of operation of Beller, withdrawal of this rejection is respectfully requested.

6. The Proposed Combination Fails To Disclose
All Of Applicants' Claimed Limitations

All claim limitations must be taught or suggested by the prior art. MPEP § 2143.03. Even if the Examiner's proposed combination and modifications were somehow proper,

Applicants' claims are still patentable because the Examiner's combination still fails to disclose all the limitations of Applicants' claims.

As discussed *supra* in Section D.1 and 2, Beller fails to teach, *inter alia*, each of the four elements of Applicants' broadest claim 22. Unger, Klaveness and Quay each fail to make up for these deficiencies.

For example, Unger, Klaveness and Quay all fail to disclose or suggest the specific dry formulation comprising a saturated phospholipid, a fatty acid, and a hydrophilic stabilizer.

Unger, Klaveness and Quay all also fails to disclose or suggest to one of ordinary skill in the art to lower the phospholipid concentration of Beller to the limitation recited in Applicants' claims.

Therefore, Applicants' broadest claim 22 is patentable over the Examiner's proposed reference combination. Thus, it follows that all of Applicants' other claims, which are all narrower in scope or add additional limitations, are all also patentable over the Examiner's references. Thus, for these additional reasons, Applicants submit that removal of this rejection is proper. MPEP § 2143.03.

II. Response To Obviousness-Type Double Patenting And Provisional Obviousness-Type Rejections

Pages 5 and 6 of the Office Action contains two rejections, the first alleging obviousness-type double patenting rejections over U.S. Patent Nos. 5,380,519 and 6,110,443 ("the '519 and '443 patents"), and the second alleging provisional obviousness-type double patenting over U.S.S.N. 09/748,120 ("the '120 application"). Applicants respectfully traverse.

Contrary to the Examiner's comments, it would not have been obvious for one of ordinary skill in the art at the time of the invention to lower the phospholipid concentration to that claimed by Applicants. In fact, conventional wisdom and any relevant teaching at the time

of the invention would seek to increase the phospholipid concentration in order to increase the number of microbubbles, and not to lower the phospholipid concentration. Applicants' phospholipid limitation is surprising and unexpected, and thus renders Applicants' claims nonobvious over the claims of the cited '510 and '443 patents. Thus, removal of this rejection is respectfully requested.

Furthermore, since the '120 application has been abandoned, this rejection is improper and removal of this rejection is respectfully requested.

To the extent the Examiner disagrees, the Examiner is respectfully requested to hold these issues in abeyance until claims are indicated to be otherwise allowable in this application.

If there are any further points requiring attention prior to allowance, the Examiner is asked to contact Applicant's counsel.

No fee is required. If there are additional fees, please charge them to our firm Deposit Account No. 14-1140.

Respectfully submitted,



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